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SYNTHESIS OF AZA-MICHAEL, MICHAEL, AND 4-HETERYL-3(2*H*)-PYRIDAZINONES FROM 4-(4-BROMOPHENYL)-4-OXO-BUT-2-ENOIC ACID

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ABSTRACT

The 4-(4-bromophenyl)-4-oxo-buta-2-enoic acid **(1)** was reacted with nitrogen and carbon nucleophiles producing the aza Michael and Michael adducts depending on the reaction medium (neutral, acidic or alkaline). Hydrazinolysis of the aza Michael adducts obtained has afforded the 4-heteryl-3(2*H*)-pyridazinone derivatives **11a-c**. The behavior of the latter compounds towards different nucleophilic and electrophilic reagents was investigated.

KEYWORDS:3-(4-Bromobenzoyl)AcrylicAcid, Aza-Michael Adducts, Michael Adducts, 4-Heteryl-3(2*H*)-Pyridazinone

INTRODUCTION

4-(4-bromophenyl)-4-oxo-buta-2-enoic acids are known as an reactive enone systems towards nitrogen containing nucleophiles.[1] They have been reported to exhibit a wide range of pharmacological activities such as aspergillus controller,[2] antibacterial[3], anticancer [4] and inhibitors of phospholipase.[5]

They are used as a key starting material due to their high electrophilicity, where the 4-(4-bromophenyl)-4-oxo-buta-2-enoic acids react readily with nitrogen and carbon nucleophiles affording either cyclic or normal Michael addition products depending on the nature of the attacking nucleophile.[6-8] Moreover, such starting material can be directed to constracting the more interesting heterocyclic compounds of important biological activities which bearing 3(2*H*)-pyridazinone moiety.[9] Recently, 3(2*H*)-pyridazinones are evaluated for their anticancer activity,[10] formyl peptide receptors (FPRs)agonists,[11] as potent and selective histamine H_3 receptor inverse antagonists.[12]

Among the wide variety of synthetic reactions the application of 4-(4-bromophenyl)-4-oxo-buta-2-enoic acid as key starting material play an important role in the functionalization and synthesis a diverse of pyridazinone derivatives with anticipated biological activity.

RESULTS AND DISCUSSIONS

Cromwell indicated by evidence that, β–benzoyl acrylic acids act as unsaturated ketones and add amines to the more reactive vinylic carbon (α-carbon to the carboxyl group) to produce the α-amino-γ-keto acid. [13] It is interesting to note that β–aroyl acrylic acids, the polarization of the double bond by the ketone qroup outweighs that caused by the carboxyl qroup.

The keto group gives a more stable carbonium ion than the carboxyl group, i.e. the α–carbon atom accept the nucleophiles (donors in Micheal condensation) more readily than the β–carbon atom. β–aroyl acrylic acids, thus, resemble α,β–unsaturated ketones in their mode of addition, (c.f. Figure 1).

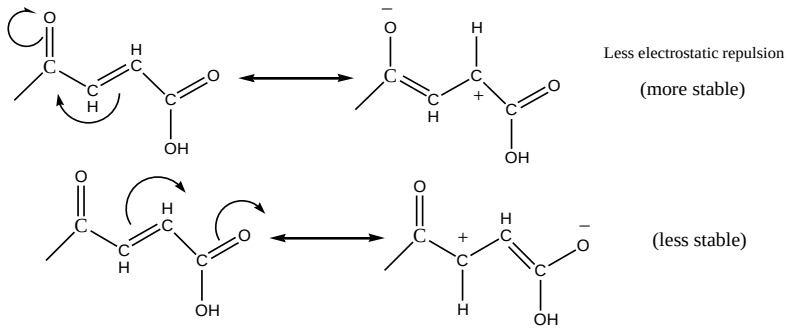


Figure 1

In this circumstance, the 4-(4-bromophenyl)-4-oxo-buta-2-enoic acid adds nucleophiles stereoselectively at β–carbon atom with respect to α,β–unsaturated ketone. Herein, the interaction of 3-(4-bromobenzoyl) acrylic acid **(1)** with pyrazoles such as 3,5-dimethylpyrazole, 3-methylpyrazol-2-en-5-one, and 3-phenyl-2-pyrazolen-5-one in neutral medium (EtOH) afforded the Aza-Michael products 2-(substituted pyrazol-1-yl)-3-(4-bromobenzoyl) acrylic acid **2a-2c**. Where the reaction involving alkylation of the pyrazole moiety by 3-(4-bromobenzoyl) acrylic acid on N(1) (*Scheme 1*).

On the other hand, when the acid **1** was submitted to react with 3-phenyl-5-oxopyrazoline in basic medium (NaOH), it afforded the Michael adduct product butyric acid **3**. In this reaction, the carbanion derived from 3-phenyl-5-oxo-pyrazoline adds to the activated double bond of the acid **1**, which reacts as α,β–unsaturated ketone rather than α,β–unsaturated acid (*C*-alkylation for substituted pyrazoline takes place under Michael reaction conditions).

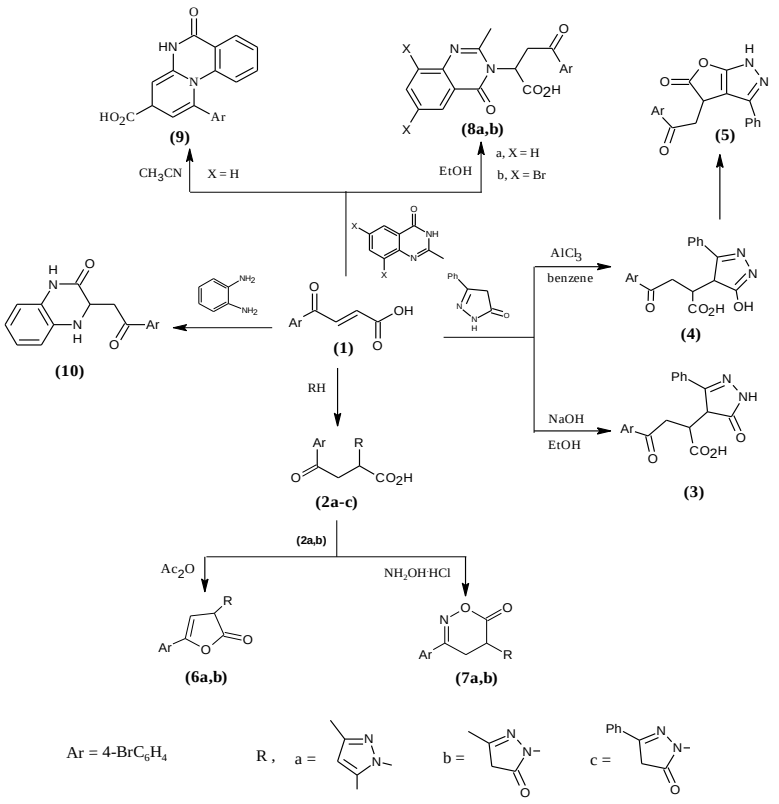
The IR spectrum of butyric acid **3** revealed strong absorption bands at 1683, 1720 cm^{-1} for keto group, the stretching and bending of NH band of pyrazole moiety appears at 3256 cm^{-1}. In ^{1}H-NMR of **3** displayed signal for NH at 9.37 (s) ppm which confirms the *C*-alkylation of the substituted pyrazoline. Also, when the above reaction was conducted in the presence of anhydrous $AlCl_3$ in boiling benzene under Friedel-Craft`s reaction conditions it yielded 2-(3-phenyl-5-hydroxypyrazolo-4-yl)-3- (4-bromobenzoyl) propionic acid **(4)** [not isolated intermediate]; which undergoes dehydration to give the furanone derivative **5** (*Scheme 1*).

Here the author concluded that the behavior of the acid **1** towards 3-phenyl-5-oxo-pyrazoline in neutral medium *N*-alkylation took place, and in basic or alkaline medium *C*-alkylation occurred, also in presence of acid medium ($AlCl_3$ is Lewis acid) *C*-alkylation obtained after aromatization of pyrazoline nucleus.

The structure of compounds **2a,b** was inferred chemically from their interaction with Ac_2O or $H_2NOH.HCl$ which furnished the furanone or 2,1-oxazinone derivatives **6a,b** or **7a,b** respectively (*Scheme 1*).

In the same fashion, interaction of β-benzoyl acrylic acid **1** with 2-methyl-4(3*H*)-quinazolinone and/or 6,8-dibromo-2-methyl-quinazolinone derivatives in boiling ethanol gave the propionic acid derivatives **8a** and/or **8b** as a product of *N*-alkylation. On the other hand, when the reaction of acid **1** with 2-methylquinazolinone was carried out in acetonitrile (aprotic solvent) the nitrogen bridge head compound **9** was yielded as a *C*-alkylation product, where the reaction involving addition of the active methyl group followed by ring closure to afford the desired product (Scheme 1). The elemental analysis and spectral data for compounds **8a**, **8b** and **9** were in well agreement with the purposed structure confirming the role of reaction medium in deriving *N*-alkylation or *C*-alkylation.

The ^{1}H-NMR spectrum of **9** displayed a signal at 4.31 (brs) ppm attributable to NH (compound **9** is a product of *C*-alkylation), while absence of any signal for NH in compounds **8a,b** (products of *N*-alkylation).



Scheme 1

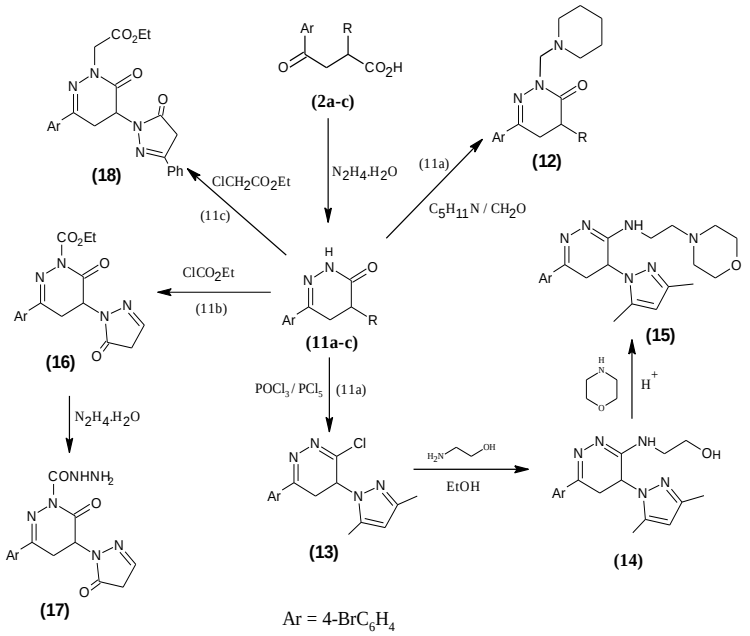
Furthermore, acrylic acid derivative **1** was allowed to react with *o*-phenylene diamine in EtOH and the 2-oxo-1,2,3,4-tetrahydroquinazoline **10** was provided (*Scheme 1*).

It was reported that,[14] non-acidic or weakly acidic NSAIDs like Celecoxib, Rofecoxib have been developed recently and have drawn the attention of medicinal chemists as they preferentially act by inhibiting COX-II enzyme and possessed lower incidence of gastric ulcers than the acidic NSAIDs which inhibit both COX-I and COX-II enzyme like Indomethacin and Aspirin. The main trend now days in pain therapy focuses on improved nonsteroidal analgesics which are effective as an analgesic but devoid of the side effects which are inherent to traditional NSAIDs.

In terms of this aspects, many studies have focused on pyridazin-3(2*H*)-ones, which are characterized by possess good analgesic and anti-inflammatory activities, beside these studies have indicated that, the heterocyclic ring substitutions at 6-position, and the presence of acetamide side chain linked to the lactam nitrogen of pyridazinone ring at the 2-position improve the analgesic and anti-inflammatory activity along with nil or very low ulcerogenicity.[15-20] Sahina et al. showed that, there is a significant dependence of the anti-inflammatory effect on the substituents at C(6) of pyridazinone ring.[21]

In the present study, the authors have designed and synthesized pyridazin-3(2*H*)-one derivatives **11a-11c** which bear heteryl moiety at the 4-position for the first time as a key starting material for a diverse pyridazine derivatives substituted at 2- and 3-position, they were achieved via hydrazinolysis of compounds **2a-2c** (*Scheme 2*).

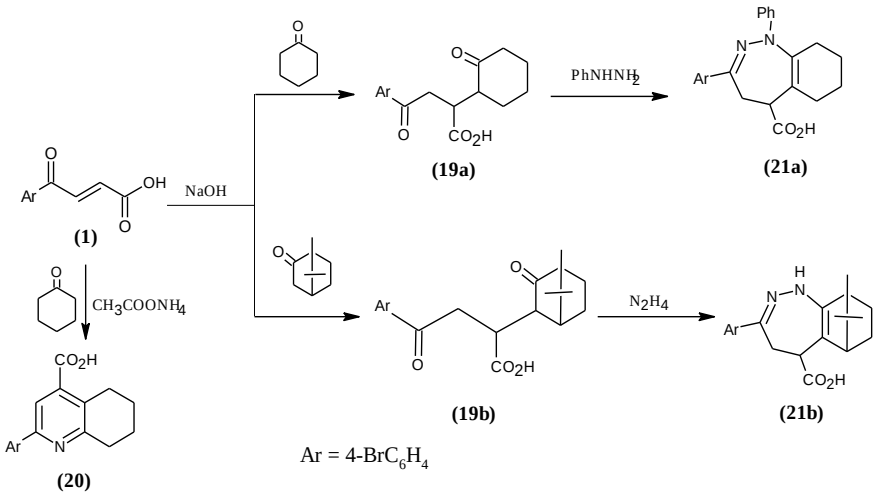
Thereafter, the pyridazin-3(2*H*)-one **11a** was submitted to react with piperidine in the presence of HCHO in MeOH under Mannich reaction conditions it yielded the 4-substituted pyridazin-3(2*H*)-one derivative **12**. On the other hand, when compound **11a** was submitted to react with $POCl_3$ in the presence of PCl_5 the desired 3-chloro derivative **13** was afforded.



Scheme 2

It was reported that, the simple replacement of chlorine atom at 4-position of quinazoline nucleus with different amines produced the amino derivatives.[22] Herein, nucleophilic substitution of the chloropyridazine derivative **13** with ethanol amine resulted in the corresponding aminopyridazine derivative **14**. The structure of compound **14** was inferred chemically by its interaction with morpholine in the presence of few drops of HCl and gave the Mannich type reaction product **15** (*Scheme 2*).

Additionally, the structure of pyridazin-3(2*H*)-one derivative **11b** was inferred chemically from its interaction with ethyl chloroformate (in accordance with reported method for electrophilic substitution of lactam form[23]) in boiling acetone in the presence of anh. K_2CO_3 to afford the 2-ethoxycarbonyl-3(2*H*)-pyridazinone **16**. This reaction takes place via tetrahedral mechanism and ethyl chloroformate reacting acid chloride rather than the ethoxy carbonyl (Cl^- is good leaving group than ethoxy group). Hydrazinolysis of the ester **16** was elaborated via its interaction with $N_2H_4.H_2O$ and the corresponding hydrazide **17** was obtained (*Scheme 3*). Moreover, pyridazinone **11c** was reacted with ethyl chloroacetate in boiling acetone and afforded 2-ethoxycarbonylmethyl-3(2*H*)-pyridazinone derivative **18** as a chemical evidence for establishment the structure of compound **11c** (*Scheme 3*).



Scheme 3

It is interesting to investigate the behavior of acrylic acid **1** towards carbon nucleophiles in different reaction medium. Thus, cyclohexanone or camphor was chosen as carbon nucleophile submitted to react with acrylic acid **1** in the presence of NaOH (basic medium) under Michael reaction conditions and the 2-substituted butyric acid derivatives **19a** and/or **19b** were afforded respectively (*Scheme 3*). When the reaction with cyclohexanone was conducted in the presence of ammonium acetate in boiling EtOH the 2-(4-bromophenyl)-4-carboxy-5,6,7,8-tetrahydroquinazoline **20** was provided (*Scheme 3*). Finally, the structure of compounds **19a,b** was inferred chemically via their hydrazinolysis. Indeed, butyric acid derivative **19a** and/or **19b** was reacted with phenylhydrazine or hydrazine hydrate and resulted to diazepine-5-carboxylic acid derivatives **21a** or **21b** respectively (*Scheme 3*).

EXPERIMETAL

General. M.P.: *Stuart* electric melting-point apparatus; uncorrected. IR spectra: λ FT-IR *Nicolet Impact 400D*; KBr pellets; υ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker* at 400 and 100 MHz, resp.; in $CDCl_3$ or (D_6) DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. DEPT135 NMR spectroscopy: used where appropriate, to aid the assignment of signals in the ^1H and ^{13}C-NMR spectra. EI-MS: *GC/MS–Qploopx Shimadzu* (Japan, 1990); in m/z. Elemental analysis was carried out in the Micro Analytical Center, Cairo University, Giza, Egypt. TLC: *Merk TLC aluminium sheets*, silica gel 60 F_{254} with detection by UV quenching at 254nm. Reagents and solvents were used as obtained from the supplier without further purification.

Compounds 2a-2c

A mixture of prop-2-enoic acid (**1)** (0.01 mol) and 3,5-dimethylpyrazole, 3-methylpyrazol-2-en-5-one, or 3-phenyl-2-pyrazolen-5-one (0.01 mol) in EtOH (50 mL) was heated under reflux for 3h. The reaction mixture was concentrated, cooled and the solid obtained was filtered off and recrystallized from $PhCH_3$: **2a-2c**.

4-(4-Bromophenyl)-2-(3,5-Dimethyl-1*h*-Pyrazol-1-yl)-4-Oxobutanoic Acid (2a)

Yield 83%. Mp 165-167 °C. IR (KBr) 1680, 1720 (CO). ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.81 (octet, 2H, CH_2), 4.83 (t, *J*=7.2Hz, 1H, methine), 5.76 (s, 1H, Pyrazole proton), 7.47-7.75 (m, 4H, Ar-H), 13.2 (brs, 1H, OH). ^{13}C NMR δ 13.8 (CH_3), 21.3 (CH_3), 34.4 (CH_2), 58.4 (CH), 102.3 (CH), 128.2 (CH), 129.2 (C), 129.5 (CH), 134.4 (C), 138.1 (C), 142.7 (C), 145.0 (C), 173.2 (C), 198.5 (C). Anal. Calc. for $C_{15}H_{15}BrN_2O_3$: C 51.30, H 4.31; found: C 51.26, H 4.29. MS: m/z 353$[M+2]^+$, 351$[M^+]$, 307, 198, 154, 105, 96.

4-(4-Bromophenyl)-2-(3-Methyl-5-Oxo-4,5-Dihydro-1*H*-Pyrazol-1-yl)-4-Oxobutanoic Acid (2b)

Yield 74%. Mp 180-181 °C. IR (KBr) 1617, 1632 (C=N), 1667, 1691, 1705 (CO). ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, CH_3), 3.09 (s, 2H, CH_2), 3.73 (octet, 2H, CH_2), 4.90 (t, *J*=7.2Hz, 1H, methine), 7.62-7.74 (m, 4H, Ar-H), 12.8 (brs, 1H, OH). ^{13}C NMR δ 16.7 (CH_3), 34.7 (CH_2), 44.3 (CH_2), 53.4 (CH), 128.9 (C), 131.5 (CH), 132.5 (CH), 135.3 (C), 154.8 (C), 168.7 (C), 171.2 (C), 199.6 (C). Anal. Calc. for $C_{14}H_{13}BrN_2O_4$: C 47.61, H 3.71; found: C 47.54, H 3.89.

4-(4-Bromophenyl)-4-Oxo-2-(5-Oxo-3-Phenyl-4,5-Dihydro-1*H* -Pyrazol-1-yl)-Butanoic Acid (2c)

Yield 81%. Mp 169 °C. IR (KBr) 1630 (C=N), 1685, 1722 (CO), 3244 (OH). ^1H NMR ($CDCl_3$): δ 3.38 (s, 2H, CH_2), 3.71 (octet, 2H, CH_2), 4.95 (t, *J*=7.3Hz, 1H, methine), 7.46-7.79 (m, 9H, Ar-H), 13.20 (brs, 1H, OH). ^{13}C-NMR δ 35.1 (CH_2), 43.6 (CH_2), 53.7 (CH), 125.2 (2CH), 126.5 (CH), 128.4 (2CH), 129.2 (C), 132.2 (2CH), 132.8 (2CH), 134.8 (C), 136.0 (C), 143.1 (C), 168.5 (C), 171.4 (C), 199.6 (C). Anal. Calc. for $C_{19}H_{15}BrN_2O_4$: C 54.96, H 3.64; found: C 55.04, H 3.59.

4-(4-Bromophenyl)-4-Oxo-2-(5-Oxo-3-Phenyl-4,5-Dihydro-1*H* -Pyrazol-4-yl)-Butanoic Acid (3)

The 3-(4-bromobenzoyl)prop-2-enoic acid **(1)** (2.55 g, 0.01 mol) was added to a stirred suspension of 3-phenyl-5-oxopyrazoline (1.60 g, 0.01 mol) and 50% sodium hydroxide(2mL) in ethanol (20 mL). The reaction mixture was stirred at room temperature for seven days, the reaction was quenched with H_2O and extracted with diethyl ether (2 × 50 mL). The combined aqueous layer was acidified by dilute hydrochloric acid. The solid that separated was filtered off, dried, and recrystallized from PhH to afford the Michael adduct **3**. Yield 66%. Mp 185-187 °C. IR (KBr) 1683, 1720 (CO), 3265 (NH). ^{1}H NMR (DMSO-d_6): δ 3.14 (t, *J*=8.4Hz, 1H, methine), 3.68 (octet, 2H, CH_2), 4.56 (d, *J*=3.1Hz, 1H, CH), 7.49-7.78 (m, 9H, Ar-H), 9.37 (s, 1H, NH), 11.40 (brs, 1H, OH). ^{13}C NMR δ 38.9 (CH), 39.6 (CH_2), 52.9 (CH), 125.6 (2CH), 127.4 (CH), 128.6 (2CH), 129.1 (C), 132.3 (2CH), 132.7 (2CH), 133.9 (C), 135.1 (C), 161.8 (C), 172.7 (C), 176.9 (C), 193.6 (C). Anal. Calc. for $C_{19}H_{15}BrN_2O_4$: C 54.96, H 3.64; found: C 55.01, H 3.68. MS: m/z 371[M^+-CO_2], 295, 218, 185, 105.

4[2-(4-Bromophenyl)-2-Oxoethyl]-3-Phenyl-1,4-Dihydro-5*H*-Furo[2,3-C]Pyrazol-5-One (5)

An equimolar mixture of 3-(4-bromobenzoyl)prop-2-enoic acid **(1)** and 3-phenyl-5-oxopyrazoline (0.01 mol), and anhydrous $AlCl_3$ (0.04 mol) in 50 mL dry benzene was heated in water bath for 3h. The reaction mixture was left overnight, and then decomposed using a mixture of ice/HCl.

The excess solvent removed by steam distillation and the crude obtained was purified by recrystallization from $PhCH_3$ to give **5**. Yield 64%. Mp 165-167 °C. IR (KBr) 1613(C=N), 1685, 1735 (CO), 3250 (NH). ^{1}H NMR ($CDCl_3$): δ 3.71 (dd, J_1=11.2Hz, J_2=16.8Hz, 2H, CH_2), 4.16 (t, *J*=11.0Hz, 1H, furanone proton), 7.54-7.90 (m, 9H, Ar-H), 10.60 (s, 1H, NH). ^{13}C NMR δ 39.7 (CH), 40.2 (CH_2), 100.5 (CH), 127.2 (CH), 127.4 (2CH), 127.8 (2CH), 129.1 (C), 130.8 (2CH), 130.9 (2CH), 132.6 (C), 137.4 (C), 170.4 (C), 195.8 (C). Anal. Calc. for $C_{19}H_{13}BrN_2O_3$: C 57.45, H 3.30; found: C 57.41, H 3.26. MS: m/z 399[M+2]$^+$, 397[M^+], 214, 138, 105, 77.

Compounds 6a,b

A solution of propionic acid **2a** and/or **2c** (0.01 mol) in 10 mL freshly distilled acetic acid anhydride was heated at 70 ^{0}C in water bath for 2h. The excess acetic acid anhydride was removed by distillation and the solid that separated after cooling was filtered off, washed with light pet. ether and recrystallized from the suitable solvent to give **6a** and **6b** respectively.

5-(4-Bromophenyl)-3-(3,5-Dimethyl-1*h*-Pyrazol-1-yl) Furan-2(3*H*)-One (6a)

Yield 91%. Mp 260-261 °C. IR (KBr) 1766 (CO). ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.42 (d, *J*=2.4Hz, 1H, CH-furanone), 5.88 (d, *J*=2.4Hz, 1H, CH-furanone), 6.06 (s, 1H, CH-imidazole), 7.34-7.57 (m, 4H, Ar-H). ^{13}C NMR δ 10.8 (CH_3), 13.7 (CH_3), 63.6 (CH), 81.9 (CH), 102.1 (CH), 123.0 (C), 127.2 (2CH), 130.1 (2CH), 137.0 (C), 139.3 (C), 142.0 (C), 144.3 (C), 175.2 (C). Anal. Calc. for $C_{15}H_{13}BrN_2O_2$: C 54.07, H 3.93; found: C 54.11, H 3.97. MS: m/z 335[M+2]$^+$, 333[M^+], 238, 156, 96.

2-[5-(4-Bromophenyl)-2-Oxo-2,3-Dihydrofuran-3-yl]-5-Phenyl-2,4-Dihydro-3*H* -Pyrazol-3-One(6b)

Yield 83%. Mp 295-296 °C. IR (KBr) 1695, 1806 (CO). ^{1}H NMR (DMSO-d_6): δ 3.38 (s, 2H, CH_2), 5.31 (d, *J*=2.4Hz, 1H, CH-furanone), 6.35 (d, *J*=2.4Hz, 1H, CH-furanone), 7.34 (t, *J*=8.1Hz, 2H, Ar-H), 7.49-7.73 (m, 7H, Ar-H). ^{13}C NMR δ 43.1 (CH_2), 62.3 (CH), 93.5 (CH), 123.1 (C), 124.8 (2CH), 126.3 (2CH), 127.5 (2CH), 127.8 (CH), 130.2 (2CH), 135.1 (C), 142.1 (C), 142.7 (C), 145.6 (C), 169.8 (C), 173.2 (C). Anal. Calc. for $C_{19}H_{13}BrN_2O_3$: C

57.45, H 3.30; found: C 57.31, H 3.17. MS: m/z 399$[M+2]^+$, 397$[M^+]$, 320, 241, 160, 77.

Compounds 7a,b

A mixture of butyric acid **2a** and/or **2c** (0.01 mol) and hydroxylamine hydrochloride (0.015 mol) in pyridine (20 mL) was heated under reflux for 3h. The reaction mixture was poured onto ice/HCl, the solid that precipitated was filtered off, washed with water and crystallized from the proper solvent to give **7a** and **7b** respectively.

3-(4-Bromophenyl)-5-(3,5-Dimethyl-1*H* -Pyrazol-1-yl)-4,5-Dihydro-6*H* -1,2-Oxazin-6-One (7a)

Yield 85%. Mp 150-152 °C. IR (KBr) 1645 (C=N), 1763 (CO). ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.82 (octet, 2H, CH_2), 5.32 (t, *J*=8.3Hz, 1H, Methine proton), 5.79 (s, 1H, pyrazole proton), 7.66-7.84 (m, 4H, Ar-H). ^{13}C NMR δ 11.2 (CH_3), 13.6 (CH_3), 32.4 (CH_2), 53.1 (CH), 100.4 (CH), 126.9 (2C), 127.1 (2CH), 131.4 (C), 135.8 (C), 139.7 (C), 163.4 (C), 169.2 (C). Anal. Calc. for $C_{15}H_{14}BrN_3O_2$: C 51.74, H 4.05; found: C 51.62, H 4.14. MS: m/z 305$[M^+-CO_2]$, 191, 156, 150, 95.

3-(4-Bromophenyl)-5-(5-Oxo-3-Phenyl-4,5-Dihydro-1*H* -Pyrazol-1-yl)-4,5-Dihydro-6*H* -1,2-Oxazin-6-One(7b)

Yield 88%. Mp 142-143 °C. IR (KBr) 1686, 1738 (CO). ^{1}H NMR ($CDCl_3$): δ 3.63 (s, 2H, CH_2), 3.85 (octet, 2H, CH_2), 5.28 (t, *J*=8.1Hz, 1H, methine proton), 7.49-7.78 (m, 9H, Ar-H). ^{13}C NMR δ 30.3 (CH_2), 41.6 (CH_2), 52.7 (CH), 125.6 (C), 126.2 (2CH), 127.4 (2CH), 128.4 (CH), 128.8 (2CH), 131.2 (2CH), 134.8 (C), 142.8 (C), 163.2 (C), 167.8 (C), 170.3 (C). Anal. Calc. for $C_{19}H_{14}BrN_3O_3$: C 55.36, H 3.42; found: C 55.19, H 3.58. MS: m/z 414$[M+2]^+$, 412$[M^+]$, 369, 255, 159, 150, 94.

Compounds 8a,b

The 3-(4-bromobenzoyl)prop-2-enoic acid **(1)** (2.55 g, 0.01 mol) was added to a stirred suspension of 2-methyl-4(3*H*)quinazolinone and/or 2-methyl-6,8-dibromo-4(3*H*)quinazolinone (0.01 mol) in ethanol (30 mL). The reaction mixture was heated under reflux for 4h. The reaction mixture was concentrated under reduced pressure and the solid that separated after cooling was filtered off, dried, and crystallized from the proper solvent to give **8a** and **8b** respectively.

4-(4-Bromophenyl)-2-(2-Methyl-4-Oxoquinazolin-3(4*H*)-yl)-4-Oxobutanoic Acid (8a)

Yield 73%. Mp 196-198 °C. IR (KBr) 1680, 1702 (CO), 3200 (OH). ^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H, CH_3), 3.84 (octet, 2H, CH_2), 5.63 (t, *J*=7.8Hz, 1H, methine proton), 7.51-7.74 (m, 8H, Ar-H), 11.84 (brs, 1H, OH). ^{13}C NMR δ 15.6 (CH_3), 36.1 (CH_2), 57.4 (CH), 118.4 (C), 124.3 (2CH), 125.9 (CH), 128.3 (CH), 128.9 (CH), 131.9 (2CH), 132.4 (CH), 135.3 (CH), 136.4 (C), 149.6 (C), 158.6 (C), 160.8 (C), 169.4 (C), 194.5 (C). Anal. Calc. for $C_{19}H_{15}BrN_2O_4$: C 54.96, H 3.64; found: C 55.12, H 3.78. MS: m/z 232, 198, 187, 105, 98.

4-(4-Bromophenyl)-2-(6,8-Dibromo-2-Methyl-4-Oxoquinazolin-3(4*H*)-yl)-4-Oxobutanoic Acid (8b)

Yield 78%. Mp 216-218 °C. IR (KBr) 1668, 1695 (CO), 3350 (OH). ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 3.82 (octet, 2H, CH_2), 5.51 (t, *J*=7.7Hz, 1H, methine proton), 7.58-7.86 (m, 6H, Ar-H), 11.84 (brs, 1H, OH). ^{13}C NMR δ 16.4 (CH_3), 36.2 (CH_2), 57.6 (CH), 117.4 (C), 118.8 (C), 129.1 (C), 129.8 (C), 131.9 (CH), 132.5 (2CH), 132.7 (2CH), 133.8 (C), 142.3 (CH), 149.6 (C), 159.8 (C), 161.1 (C), 169.4 (C), 196.2 (C). Anal. Calc. for $C_{19}H_{13}Br_3N_2O_4$: C 39.82, H 2.29; found: C 39.95, H 2.34. MS: m/z 376(M^+-Br-C_6H_4-$COCH_2$), 244, 201, 105, 77.

1-(4-Bromophenyl)-6-Oxo-5,6-Dihydro-3*H*-Pyrido[1,2-a]Quinazoline-3-Carboxylic Acid (9)

A mixture of 3-(4-bromobenzoyl)prop-2-enoic acid **(1)** (2.55 g, 0.01 mol) and 2-methyl-4(3*H*)quinazolinone (1.60 g, 0.01 mol) in acetonitrile (30 mL) was treated with piperidine (few drops) and heated at 60 °C for 2h. The reaction mixture was diluted with water, the solid that separated was filtered off and recrystallized from toluene to afford **9**. Yield 71%. Mp 145-146 °C. IR (KBr) 1653, 1703 (CO), 3421 (OH). ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 1H, methine proton), 4.21 (brs, 1H, NH), 6.96-8.02 (m, 10H, Ar-H), 13.16 (brs, 1H, OH). ^{13}C NMR δ 48.7 (CH), 102.1 (CH), 104.6 (CH), 118.2 (CH), 120.2 (C), 120.7 (CH), 125.5 (C), 129.2 (CH), 129.8 (2CH), 130.2 (2CH), 134.5 (C), 135.2 (CH), 137.6 (C), 140.8 (C), 145.0 (C), 160.9 (C), 176.3 (C). Anal. Calc. for $C_{19}H_{13}BrN_2O_3$: C 57.45, H 3.30; found: C 57.39, H 3.37. MS: m/z 337(M^+- CO_2 , OH), 180, 156, 105, 94.

3-[2-(4-Bromophenyl)-2-Oxoethyl]-3,4-Dihydroquinoxalin-2(1*H*)-One (10)

A mixture of 3-(4-bromobenzoyl)prop-2-enoic acid **(1)** (2.55 g, 0.01 mol) and *o*-phenylenediamine (1.08 g, 0.01 mol) in ethanol (30 mL) was heated under reflux for 4h. The solid that separated after cooling was filtered off, dried, and crystallized from ethanol to give the quinoxalinone **10**. Yield 83%. Mp 158-159 °C. IR (KBr) 1673, 1685 (CO), 3100 (NH). ^{1}H NMR (DMSO-d_6): δ 3.62 (octet, 2H, CH_2), 4.87 (dd, J_1=9.2Hz, J_2=2.7Hz, 1H, methine proton), 7.06-7.816 (m, 8H, Ar-H), 9.78 (brs, 1H, NH), 11.96 (brs, 1H, NH-amide). ^{13}C NMR δ 34.3 (CH_2), 57.2 (CH), 117.2 (CH), 117.8 (CH), 121.7 (CH), 122.5 (CH), 128.3 (C), 130.0 (C), 133.2 (2CH), 133.4 (2CH), 136.6 (C), 140.3 (C), 164.7 (C), 193.7 (C). Anal. Calc. for $C_{16}H_{13}BrN_2O_2$: C 55.67, H 3.80; found: C 55.60, H 3.73. MS: m/z 347$[M+2]^+$, 345 M^+, 198, 147, 130.

Pyridazinones 11a-c

Hydrazine hydrate (0.015 mol) was added to a stirred solution of butyric acids **2a-c** (0.01 mol) in ethanol (30 mL) and the reaction mixture was heated under reflux for 3h. The reaction mixture was concentrated under reduced pressure and the solid that separated after cooling was filtered off, dried, and crystallized from the proper solvent to give pyridazinones **11a-c**.

6-(4-Bromo-Phenyl)-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydro-2*H* -Pyridazin-3-One (11a)

Yield 92%. Mp 209-211 °C. IR (KBr) 1651 (C=N), 1674 (CO), 3202(NH). ^{1}H NMR (DMSO-d_6): δ 2.17 (s, 6H, $2CH_3$), 4.05 (octet, 2H, CH_2), 5.37 (t, J=7.9Hz, 1H, methine proton), 5.68 (s, 1H, CH-pyrazole), 7.53 (d, J=8.1, 2H, Ar-H), 7.69 (d, J=8.1, 2H, Ar-H), 10.71 (brs, 1H, NH). ^{13}C NMR δ 13.8 (CH_3), 16.7 (CH_3), 33.9 (CH_2), 55.9 (CH), 105.7 (CH), 126.3 (C), 130.2 (2CH), 132.8 (2CH), 137.2 (C), 138.6 (C), 150.6 (C), 154.0 (C), 163.4 (C). Anal. Calc. for $C_{15}H_{15}BrN_4O$: C 51.89, H 4.35; found: C 51.78, H 4.43. MS: m/z 268[M^+-Br], 250, 224, 195, 143, 115.

6-(4-Bromo-Phenyl)-4-(3-Methyl-5-oxo-4,5-Dihydro-Pyrazol-1-yl)-4,5-Dihydro-2*H* -Pyridazin-3-One (11b)

Yield 86%. Mp 230-232 °C. IR (KBr) 1651(C=N), 1673 (CO), 3228, 3322 (NH). ^{1}H NMR (DMSO-d_6): δ 1.97 (s, 3H, CH_3), 3.32 (s, 2H, CH_2-pyrazole), 3.87 (octet, 2H, CH_2), 4.92 (t, J=7.9Hz, 1H, methine proton), 7.67-7.71 (m, 4H, Ar-H), 11.71 (brs, 1H, NH). ^{13}C NMR δ 19.3 (CH_3), 32.6 (CH_2), 44.8 (CH_2), 54.6 (CH), 125.3 (C), 130.6 (2CH), 132.4 (2CH), 136.8 (C), 158.8 (C), 160.0 (C), 162.3 (C), 168.8 (C). Anal. Calc. for $C_{14}H_{13}BrN_4O_2$: C 48.16, H 3.75; found: C 48.09, H 3.79.

6-(4-Bromo-Phenyl)-4-(5-Oxo-3-Phenyl-4,5-Dihydro-Pyrazol-1-yl)-4,5-Dihydro-2*H* -Pyridazin-3-One (11c)

Yield 84%. Mp 238-240 °C. IR (KBr) 1650 (C=N), 1679 (CO), 3200 (NH). ^{1}H NMR (DMSO-d_6): δ 3.58 (s, 2H, CH_2), 3.76 (octet, 2H, CH_2), 5.13 (t, J=7.9Hz, 1H, methine proton), 7.46-7.56 (m, 9H, Ar-H), 11.86 (brs, 1H, NH).

^{13}C NMR δ 32.6 (CH_2), 44.2 (CH_2), 55.3 (CH), 125.7 (C), 126.9 (2CH), 127.7 (2CH), 129.4 (CH), 130.8 (2CH), 133.1 (2CH), 136.7 (C), 136.8 (C), 154.0 (C), 158.5 (C), 161.9 (C), 168.4 (C). Anal. Calc. for $C_{19}H_{15}BrN_4O_2$: C 55.49, H 3.68; found: C 55.69, H 3.79.

6-(4-Bromo-Phenyl)-4-(3,5-Dimethyl-Pyrazol-1-yl)-2-Piperidin-1-yl-Methyl-4,5-Dihydro-2*H* -Pyridazin-3-One (12)

A mixture of pyridazinone **11a** (3.47 g, 0.01 mol), piperidine (0.85 g, 0.01 mol), and formaldehyde (1 ml) in 30 mL ethanol was stirred at room temperature for 5min. and few drops of HCl was added. The reaction mixture was heated at 65^{0}C for 6h. The excess solvent was removed by vacuum distillation, the residue was washed by cold water and recrystallized from ethanol/water to afford **12**. Yield 72%. Mp 185-187 $^{\circ}$C. IR (KBr) 1682 (CO). ^{1}H NMR (DMSO-d_6): δ 1.23-1.27 (m, 6H, $3CH_2$), 2.17 (s, 6H, $2CH_3$), 2.34-2.38 (m, 4H, $2CH_2$), 4.17 (s, 2H, CH_2), 4.38 (octet, 2H, CH_2-Pyridazine), 5.47 (t, *J*=7.9Hz, 1H, methine proton), 7.41-7.53 (m, 4H, Ar-H). ^{13}C NMR δ 13.4 (CH_3), 15.8 (CH_3), 26.3 (CH_2), 28.0 (CH_2), 33.6 (CH_2), 51.7 ($2CH_2$), 55.1 (CH), 77.4 (CH_2), 105.3 (CH), 124.6 (C), 130.4 (2CH), 133.3 (2CH), 138.6 (C), 138.9 (C), 151.6 (C), 157.1 (C), 164.3 (C). Anal. Calc. for $C_{21}H_{26}BrN_5O$: C 56.76, H 5.90; found: C 56.45, H 5.81. MS: m/z 346[M^+-$C_6H_{12}N$], 281, 191, 156, 84.

6-(4-Bromo-Phenyl)-3-Chloro-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydro-Pyridazine (13)

A solution of pyridazinone derivative **11a** (3.47 g, 0.01 mol) and 1 g of phosphorus pentachloride in phosphorus oxychloride (20 mL) was heated in water bath at 70 ^{0}C for 2h. The reaction mixture was cooled and diluted with ice water and the resulted precipitate was collected by filtration and crystallized from toluene to give **13**. Yield 81%. Mp 181-183 $^{\circ}$C. ^{1}H NMR (DMSO-d_6): δ 2.03 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.85 (d, *J*=7.9Hz, 2H, CH_2-Pyridazine), 5.36 (t, *J*=7.9Hz, 1H, methine proton), 5.87 (s, 1H, CH-pyrazole), 7.49-7.79 (m, 4H, Ar-H). ^{13}C NMR δ 12.9 (CH_3), 15.6 (CH_3), 32.9 (CH_2), 54.0 (CH), 101.2 (CH), 126.4 (C), 132.1 (2CH), 133.7 (2CH), 138.4 (C), 140.1 (C), 153.8 (C), 154.5 (C), 165.0 (C). Anal. Calc. for $C_{15}H_{14}BrClN_4$: C 49.27, H 3.86; found: C 49.12, H 3.89. MS: m/z 332[M^++2 - Cl], 330, 175, 156, 95.

2-[6-(4-Bromo-Phenyl)-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydro-Pyridazin-3-yl-Amino]-Ethanol (14)

A solution of chloropyridazine **13** (3.66 g, 0.01 mol) and ethanolamine (0.92 g, 0.015 mol) in *n*-butanol (20 mL) was heated under reflux for 4h. The reaction mixture was leaved overnight, the solid that separated was collected and recrystallized from *n*-butanol to give 1**4**. Yield 64%. Mp 204-205 $^{\circ}$C. IR (KBr) 1613, 1651 (C=N), 1679 (CO), 3424 (NH) and/or (OH). ^{1}H NMR (DMSO-d_6): δ 2.06 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.51 (t, *J*=6.4Hz, 2H, NH$\underline{CH_2}$), 3.67 (octet, 2H, CH_2), 3.75 (t, *J*=6,4Hz, 2H, $\underline{CH_2}$OH), 4.83 (brs, 1H, OH), 5.32 (t, *J*=7.9Hz, 1H, methine proton), 5.81 (s, 1H, CH-pyrazole), 7.53-7.68 (m, 4H, Ar-H), 9.62 (brs, 1H, NH). ^{13}C NMR δ 12.8 (CH_3), 15.1 (CH_3), 32.3 (CH_2), 49.6 (CH), 50.3 (CH_2), 60.7 (CH_2), 101.5 (CH), 126.1 (C), 131.9 (2CH), 134.7 (2CH), 137.8 (C), 138.0 (C), 154.1 (C), 155.0 (C), 164.5 (C). Anal. Calc. for $C_{17}H_{20}BrClN_5O$: C 52.32, H 5.17; found: C 52.48, H 5.24. MS: m/z 592[M+2]$^+$, 590[M^+], 330, 236, 156, 95, 60.

[6-(4-Bromo-Phenyl)-4-(3,5-Dimethyl-Pyrazol-1-yl)-4,5-Dihydro-Pyridazin-3-yl]-(2-Morpholin-4-yl-Ethyl)-Amine (15)

A mixture of pyridazine **14** (5.90 g, 0.01 mol), morpholine (1.30 g, 0.015 mol), and 0.5 mL of conc. HCl in ethanol (30 mL) was heated under reflux for 3h. The reaction mixture was concentrated under vacuum and the solid that separated out was filtered off, dried and recrystallized from ethanol to give pyridazine **15**. Yield 83%. Mp 130-132 $^{\circ}$C. IR (KBr) 1632 (C=N), 3298 (NH). ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.40-2.46 (m, 4H, $2CH_2$), 3.34

(t, *J*=6.1Hz, 2H, $\underline{CH_2}$-morpholino), 3.41-3.46 (m, 4H, $2CH_2$), 3.56 (t, *J*=6.1Hz, 2H, $NH\underline{CH_2}$), 3.77 (octet, 2H, CH_2), 5.21 (t, *J*=7.9Hz, 1H, methine proton), 5.76 (s, 1H, CH-pyrazole), 7.49-7.63 (m, 4H, Ar-H), 9.84 (brs, 1H, NH). ^{13}C NMR δ 12.9 (CH_3), 15.0 (CH_3), 32.5 (CH_2), 44.7 (CH_2), 52.7 (CH), 56.1 ($2CH_2$), 57.2 (CH_2), 67.8 ($2CH_2$), 100.9 (CH), 126.4 (C), 130.3 (2CH), 133.0 (2CH), 137.6 (C), 139.9 (C), 153.5 (C), 157.0 (C), 163.8 (C). Anal. Calc. for $C_{21}H_{27}BrN_6O$: C 54.91, H 5.92; found: C 55.08, H 5.98. MS: m/z 461$[M+2]^+$, 459$[M^+]$, 330, 236, 156,130, 95.

3-(4-Bromo-Phenyl)-5-(3-Methyl-5-Oxo-4,5-Dihydro-Pyrazol-1-yl)-6-Oxo-5,6-Dihydro-4*H*-Pyridazine-1-Carboxylic Acid Ethyl Ester (16)

A mixture of pyridazinone derivative **11b** (3.49 g, 0.01 mole), ethylchloroformate (5.05 g, 0.05 mole), and anhydrous K_2CO_3 (5 g, 0.04 mole) in dry acetone (60 mL) was heated at 60 °C for 48h. Excess solvent was removed by distillation and water was added upon the reaction mixture. The reaction mixture was partitioned between H_2O and diethyl ether and the liquid phase was extracted 3x with 30mL Et_2O. The combined organic extracts were dried by sodium sulphate and the solvent was removed by distillation at atmospheric pressure. The solid obtained was crystallized from ethanol to give **16**. Yield 74%. Mp 110-112 °C. IR (KBr) 1696, 1753 (CO). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J*=8.7Hz, 3H, $OCH_2\underline{CH_3}$), 2.09 (s, 3H, CH_3), 3.16 (s, 2H, CH_2), 3.72 (octet, 2H, CH_2), 4.16 (q, *J*=3.4Hz, 2H, $O\underline{CH_2}CH_3$), 4.47 (t, *J*=7.9Hz, 1H, methine proton), 7.49-7.68 (m, 4H, Ar-H). ^{13}C NMR δ 15.3 (CH_3), 17.1 (CH_3), 37.0 (CH_2), 44.7 (CH_2), 53.4 (CH), 64.8 (CH_2), 123.6 (C), 129.8 (2CH), 131.2 (2CH), 138.8 (C), 146.1 (C), 161.0 (C), 163.7 (C), 165.5 (C), 167.8 (C). Anal. Calc. for $C_{17}H_{17}BrN_4O_4$: C 48.47, H 4.07; found: C 48.58, H 4.12. MS: m/z 348$[M^+ - CO_2, CH_2{=}CH_2]$, 348, 270, 193, 156, 95, 76.

3-(4-Bromo-Phenyl)-5-(3-Methyl-5-Oxo-4,5-Dihydro-Pyrazol-1-yl)-6-Oxo-5,6-Dihydro-4*H*-Pyridazine-1-Carboxylic Acid Hydrazide (17)

A solution of pyridazinone derivative **16** (4.21 g, 0.01 mol) and hydrazine hydrate (0.075 g, 0.015 mol) in methanol (30 mL) was heated under reflux for 3h. The reaction mixture was concentrated under reduced pressure and the solid that separated after cooling was filtered off, dried, and crystallized from methanol to give the hydrazide **17**. Yield 82%. Mp 218-220 °C. IR (KBr) 1650 (C=N), 1676 (CO), 3228, 3310 (NH). ^{1}H NMR (DMSO-d_6): δ 2.07 (s, 3H, CH_3), 3.17 (s, 2H, CH_2), 3.76 (octet, 2H, CH_2), 4.05 (brs, 1H, NH), 4.91 (t, *J*=8.1Hz, 1H, methine proton), 7.47-7.59 (m, 4H, Ar-H), 9.87 (brs, 2H, NH_2). ^{13}C NMR δ 18.4 (CH_3), 35.4 (CH_2), 43.8 (CH_2), 50.6 (CH), 123.8 (C), 128.7 (2CH), 130.9 (2CH), 135.3 (C), 145.0 (C), 157.6 (C), 162.4 (C), 163.0 (C), 168.3 (C). Anal. Calc. for $C_{15}H_{15}BrN_6O_3$: C 44.24, H 3.71; found: C 44.06, H 3.62. MS: m/z 409$[M+2]^+$, 407$[M^+]$, 348, 193, 156, 105, 59.

[3-(4-Bromo-Phenyl)-6-oxo-5-(5-oxo-3-Phenyl-4,5-Dihydro-Pyrazol-1-yl)-5,6-Dihydro-4H-Pyridazin-1-yl]-Aceticacid Ethyl ester (18)

The same procedure used for **16**, using a mixture of pyridazinone derivative **11c** (4.11 g, 0.01 mole), ethylchloroacetate (6.13 g, 0.05 mole), and anhydrous K_2CO_3 (5 g, 0.04 mole) in dry acetone (60 mL). The crude solid was crystallized from Pet ether100-120°C to afford **18**. Yield 69%. Mp 120-121 °C. IR (KBr) 1685, 1734 (CO). ^{1}H NMR (DMSO-d_6): δ 1.23 (t, *J*=6.7Hz, 3H, CH_3), 3.76 (octet, 2H, CH_2), 3.67 (s, 2H, CH_2-pyrazole), 4.16 (q, *J*=6.7Hz, 2H, $O\underline{CH_2}CH_3$), 4.84 (s, 2H, $O\underline{CH_2}COO$), 4.87 (t, *J*=8.1Hz, 1H, methine proton), 7.37-7.61 (m, 9H, Ar-H). ^{13}C NMR δ 13.9 (CH_3), 32.3 (CH_2), 45.1 (CH_2), 47.0 (CH_2), 52.6 (CH), 66.3 (CH_2), 123.4 (C), 124.1 (2CH), 124.7 (2CH), 128.1 (CH), 129.6 (2CH), 130.8 (2CH), 136.4 (C), 138.2 (C), 153.0 (C), 157.8 (C), 162.0 (C), 166.3 (C), 168.0 (C). Anal. Calc. for $C_{23}H_{21}BrN_4O_4$: C 55.54, H 4.26; found: C 55.65, H 4.32. MS: m/z 499$[M+2]^+$, 497$[M^+]$, 423, 411, 331, 254, 159.

Compounds 19a,b

A mixture of propenoic acid **1** (2.55 g, 0.01 mol), cyclohexanone and/or camphor (0.01 mol), and aqueous solution of sodium hydroxide (2 mL, 50%) in ethanol (20 mL) was stirred at room temperature for seven days. The reaction mixture was diluted with water and then extracted from ether to get ride from neutral material. The aqueous layer was acidified with ice/dilute HCl. The semisolid material was extracted from ether, dried, slow evaporation and the solid obtained was crystallized from the proper solvent to give **19a,b**.

4-(4-Bromo-Phenyl)-4-Oxo-2-(2-Oxo-Cyclohexyl)-Butyric Acid (19a)

Yield 57%. Mp 160-162 °C. IR (KBr) 1680, 1704, 1720 (CO), 3422 (OH). ^{1}H NMR (DMSO-d_6): δ 1.34-1.73 (m, 6H, hexyl proton), 2.03-2.27 (m, 2H, hexyl proton), 3.12 (sextet, 1H, CHCOOH), 3.41 (octet, 2H, CH_2), 3.53-3.57 (m, 1H, hexyl proton), 7.42-7.56 (m, 4H, Ar-H), 11.30 (brs, 1H, OH). ^{13}C NMR δ 20.8 (CH_2), 24.3 (CH_2), 24.7 (CH_2), 36.9 (CH_2), 38.0 (CH), 38.8 (CH_2), 51.6 (CH), 129.2 (C), 130.3 (2CH), 131.8 (2CH), 135.5 (C), 178.2 (C), 194.3 (C), 208.1 (C). Anal. Calc. for $C_{16}H_{17}BrO_4$: C 54.41, H 4.85; found: C 54.25, H 4.67. MS: m/z 292[M^+- CO_2, OH], 156, 137, 105, 81.

4-(4-Bromo-Phenyl)-4-Oxo-2-(4,7,7-Trimethyl-3-oxo-Bicyclo[2.2.1]Hept-2-yl)-Butyric Acid (19b)

Yield 64%. Mp 197-198 °C. IR (KBr) 1691, 1710, 1759 (CO), 3363 (OH). ^{1}H NMR (DMSO-d_6): δ 0.96 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.26 (s, 3H, CH_3),1.48-1.71 (m, 4H, $2CH_2$), 1.87 (t, J=9.7, 1H, hexyl-H), 3.10 (sextet, 1H, CH), 3.35 (octet, 2H, CH_2), 3.62-3.68 (m, 1H, hexyl-H), 7.48-7.56 (m, 4H, Ar-H), 11.34 (brs, 1H, OH). ^{13}C NMR δ 11.9 (CH_3), 18.2 (CH_3), 18.6 (CH_3), 21.9 (CH_2), 26.8 (CH_2), 37.3 (CH_2), 38.4 (CH), 44.6 (CH), 45.7 (CH), 48.4 (C), 56.8 (C), 129.4 (C), 130.0 (2CH), 130.7 (2CH), 135.9 (C), 178.4 (C), 195.0 (C), 213.1 (C). Anal. Calc. for $C_{20}H_{23}BrO_4$: C 58.98, H 5.69; found: C 59.15, H 5.87. MS: m/z 346[M^+- CO_2, OH], 267, 175, 156, 137.

2-(4-Bromo-Phenyl)-5,6,7,8-Tetrahydro-Quinoline-4-Carboxylic Acid (20)

A mixture of propenoic acid 1 (2.55 g, 0.01 mol), cyclohexanone (0.98 g, 0.01 mol), and ammonium acetate (5 g) in ethanol (50 mL) was heated at 70 °C for 8h. The reaction mixture was concentrated under vacuum and the solid that separated out was filtered off, dried and recrystallized from toluene to give quinazoline **20**. Yield 53%. Mp 203-205 °C. IR (KBr) 1687 (CO), 3420 (OH). ^{1}H NMR (DMSO-d_6): δ 1.34-1.63 (m, 4H, $2CH_2$), 2.42-2.56 (m, 2H, CH_2), 3.33-3.51 (m, 2H, CH_2), 7.33-7.78 (m, 5H, Ar-H), 10.81 (brs, 1H, OH). ^{13}C NMR δ 23.7 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 27.3 (CH_2), 120.7 (CH), 126.1 (C), 130.5 (C), 133.1 (2CH), 133.4 (2CH), 134.6 (C), 156.4 (C), 161.8 (C), 169.4 (C). Anal. Calc. for $C_{16}H_{14}BrNO_2$: C 57.85, H 4.25; found: C 57.71, H 4.37. MS: m/z 287[M^+- CO_2], 208, 156, 132, 77.

Compounds 21a,b

A mixture of Michael adducts **19a** and/or **19b** (0.01 mol) and hydrazine hydrate and/or phenyl hydrazine (0.01 mol) in ethanol (30 mL) was heated under reflux for 6h. The solid that separated after cooling was filtered off, dried, and recrystallized from ethanol to give **21a** and **21b** respectively.

3-(4-Bromo-Phenyl)-1-Phenyl-4,5,6,7,8,9-Hexahydro-1*H*-Benzo[*c*][1,2]Diazepine-5-Carboxylic Acid(21a)

Yield 84%. Mp 140-141 °C. IR (KBr) 1620 (C=N), 1707 (CO), 3390(OH). ^{1}H NMR (DMSO-d_6): δ 1.36-1.45 (m, 2H, CH_2), 1.67-1.89 (m, 4H, $2CH_2$), 2.10-2.26 (m, 2H, CH_2), 3.16 (octet, 2H, CH_2), 3.84 (dd, J_1=7.7Hz, J_2=3.4Hz, 1H, methine proton), 6.81-7.42 (m, 4H, Ar-H), 10.65 (brs, 1H, OH). ^{13}C NMR δ 22.6 (CH_2), 26.1 (CH_2), 27.4 (CH_2), 31.8 (CH_2), 40.7 (CH_2), 46.8 (CH), 112.7 (C), 117.8 (2CH), 121.4 (C), 123.1 (CH), 128.3 (2CH), 131.6 (2CH), 135.0 (C), 137.0 (C), 144.9 (C), 147.2 (C), 171.3 (C). Anal. Calc. for $C_{22}H_{21}BrN_2O_2$: C 62.13, H 4.98; found: C 62.26, H 4.74. MS: m/z

379[M^+- CO_2], 303, 228, 156, 149, 105.

3-(4-Bromo-Phenyl)-9,10,10-Trimethyl-4,5,6,7,8,9-Hexahydro-1*H*-6,9-Methano-Benzo[*c*][1,2]Diazepine-5 Carboxylic Acid (21b)

Yield 87%. Mp 129-131 °C. IR (KBr) 1611 (C=N), 1732 (CO), 3143 (NH), 3402 (OH). ^{1}H NMR (DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.42-1.54 (m, 2H, CH_2), 1.71-1.79 (m, 2H, CH_2), 2.47 (octet, 2H, CH_2), 2.81 (t, J=9.4Hz, 1H, hexyl-H), 3.56 (dd, J_1=7.6Hz, J_2=3.4Hz, 1H, CH), 7.51-7.58 (m, 4H, Ar-H), 9.84 (brs, 1H, NH), 10.73 (brs, 1H, OH). ^{13}C NMR δ 14.1 (CH_3), 18.4 (CH_3), 20.8 (CH_3), 22.3 (CH_2), 30.7 (CH_2), 40.8 (CH_2), 44.1 (CH), 45.9 (CH), 50.9 (C), 52.2 (C), 120.6 (C), 122.6 (C), 130.9 (2CH), 131.4 (2CH), 136.5 (C), 145.8 (C), 150.0 (C), 171.1 (C). Anal. Calc. for $C_{20}H_{23}BrN_2O_2$: C 59.56, H 5.75; found: C 59.70, H 5.47.

CONCLUSION

The present work has succeeded to study the effect of the medium pH (neutral, acidic, or basic) on the type of Michael addition (Michael or Aza-Michael addition) beside studying the behavior of 3-(4-bromobenzoyl) acrylic acid towards nitrogen and carbon nucleophiles producing a series of 3(2*H*)-pyridazinone derivatives bearing 4-heteryl moiety.

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